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Review

REVIEW

# Extracellular matrix glycation and receptor for advanced glycation end-products activation: a missing piece in the puzzle of the association between diabetes and cancer

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## Abstract

A growing body of epidemiologic evidence suggests that people with diabetes are at a significantly higher risk of many forms of cancer. However, the molecular mechanisms underlying this association are not fully understood. Cancer cells are surrounded by a complex milieu, also known as tumor microenvironment, which contributes to the development and metastasis of tumors. Of note, one of the major components of this niche is the extracellular matrix (ECM), which becomes highly disorganized during neoplastic progression, thereby stimulating cancer cell transformation, growth and spread. One of the consequences of chronic hyperglycemia, the most frequently observed sign of diabetes and the etiological source of diabetes complications, is the irreversible glycation and oxidation of proteins and lipids leading to the formation of the advanced glycation end-products (AGEs). These compounds may covalently crosslink and biochemically modify structure and functions of many proteins, and AGEs accumulation is particularly high in long-living proteins with low biological turnover, features that are shared by most, if not all, ECM proteins. AGEs-modified proteins are recognized by AGE-binding proteins, and thus glycated ECM components have the potential to trigger Receptor for advanced glycation end-products-dependent mechanisms. The biological consequence of receptor for advanced glycation end-products activation mechanisms seems to be connected, in different ways, to drive some hallmarks of cancer onset and tumor growth. The present review intends to highlight the potential impact of ECM glycation on tumor progression by triggering receptor for advanced glycation end-products-mediated mechanisms.

## Introduction

The association between diabetes and cancer was firstly described more than a century ago by Maynard and Pearson (1,2). At present, an extensive body of epidemiological studies suggests that people with diabetes have an increased risk of developing certain cancer types (3,4), after adjusting for age and other confounding factors such as obesity. Furthermore, patients with diabetes who develop cancer have even a worse prognosis after treatment with chemotherapy or surgery as well as a higher mortality risk than subjects without diabetes (5–7). Even more, chronic hyperglycemia, measured by glycated hemoglobin levels also correlates with increased risk for a number of cancers, independently of the onset of diabetes (8). In 2010, the American Diabetes Association published a consensus report, highlighting the importance of hyperglycemia as a relevant mediator in the association between diabetes and cancer (9). However, although hyperglycemia is one of the most widely studied metabolic alterations in diabetes mellitus, the effects of hyperglycemia on cancer have received much less attention.

In the late 80's and early 90's cumulative evidences derived from both experimental and clinical studies pointed to prolonged exposure to hyperglycemia is the primary factor associated with the development of most diabetic complications. Thus, the magnitude and duration of target tissue exposure to abnormally high levels of blood glucose correlate closely with

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**Abbreviations**

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|---|---|
| AGE | advanced glycation end-products |
| ECM | extracellular matrix |
| EMT | epithelial–mesenchymal transition |
| miRNA | microRNA |
| TGF | transforming growth factor |

the extent and rate of progression of retinopathy, nephropathy and neuropathy (10–12).

The formation of AGEs, by the so-called Maillard reaction, is a complex cascade of glycation reactions of different kinds of biomolecules including proteins, lipids and nucleic acids. In the Maillard reaction, an amine moiety from amines, amino acids, peptides or proteins reacts with a carbonyl group, present not only in reducing sugars such as glucose but also in oxidized lipids. The formation of AGEs occurs through different steps, where the formation of a Schiff base, by a non-enzymatic reaction, is highly dependent on the concentrations of reducing sugars or oxidized lipids. Later, this Schiff base undergoes some chemical rearrangements leading to the formation of slowly reversed Amadori products, also known as early glycation products. These Amadori products can then be converted through complex rearrangement reactions to a chemically related group of moieties, termed AGEs, which can irreversibly bind to proteins (13,14).

AGEs are not only long-term markers of elevated glucose; they are active mediators of tissue pathology through two main mechanisms. Firstly, AGEs may covalently crosslink and biochemically modify structure and functions of many proteins, including the components of the two main types of ECM, the interstitial connective tissue matrix, and the basement membrane. Additionally, all these AGEs-modified proteins are recognized by several advanced glycation end-products (AGEs)-binding proteins, among which receptor for advanced glycation end-products (RAGE, also known as AGER, see Figure 1) is associated to trigger proinflammatory intracellular signaling cascades once it is engaged by AGEs, leading to consistent and robust cellular responses (15,16).

At present, compelling evidences demonstrate that fueling inflammation in the tumor microenvironment creates a tumor-promoting milieu which, in turn, favors proliferation and survival of cancer cells, alters the immune response and promotes angiogenesis and metastasis (17,18).

In this context, emerging experimental data suggest that the multiligand RAGE axis may be an important contributor to this tumor-promoting inflammatory milieu (19), and thereby promoting the proliferation, new vessel network formation, invasiveness of tumor cell and the formation of distant metastasis (20).

Although, a growing body of evidence has established a strong association of RAGE over-expression with the malignant potential of various cancer types as well as the role of different RAGE ligands highly abundant at the tumor microenvironment (20–22), a missing element and not less important, still remains to be studied in the complex puzzle denoted by the association between diabetes and cancer: the glycation of the extracellular matrix (ECM). The non-enzymatic reaction that results in glycated ECM components can be seen as a reservoir with the potential to generate a multitude of RAGE-dependent mechanisms.

## Advanced glycation and ECM dysfunction

ECM is mainly formed by a large variety of macromolecules whose precise composition and specific structures vary from tissue to tissue. Two main classes of extracellular macromolecules make up the matrix: (1) polysaccharide chains of the class called glycosaminoglycans, which are usually found covalently linked to protein in the form of proteoglycans, and (2) fibrous proteins. These fibrous-forming proteins, including collagen, elastin, fibronectin and laminin, have both structural and adhesive functions (23).

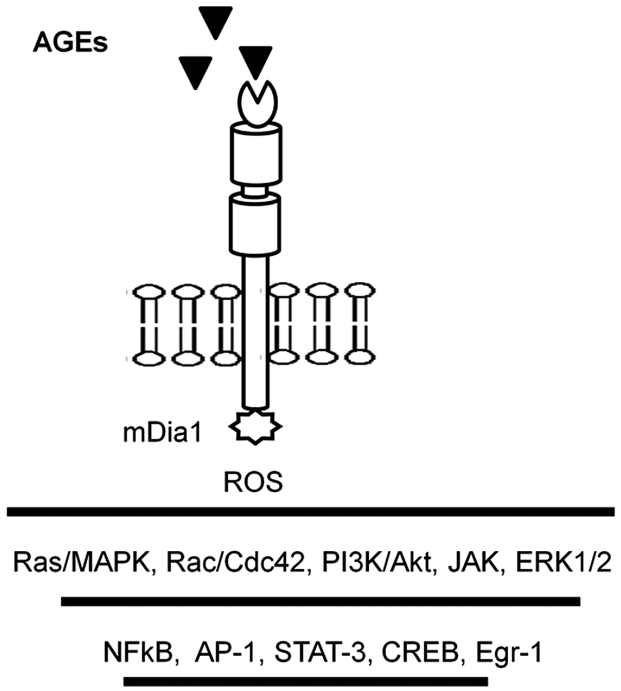


**Figure 1.** The receptor of advanced glycation end-products (RAGE) is associated to trigger proinflammatory intracellular signaling cascades once it is engaged by AGEs, leading to consistent and robust cellular responses. Once engaged, multiple signaling pathways are triggering, including reactive oxygen species (ROS), p21ras, erk1/2 (p44/p42) MAP kinases, p38 and SAPK/JNK MAP kinases, rhoGTPases, phosphoinositol-3 kinase and the JAK/STAT pathway, with important downstream inflammatory consequences such as activation of NF-κB, AP-1 and Stat-3. The cytoplasmic domain of RAGE is essential for RAGE ligand-triggered signal transduction where a key binding partner of this domain is the mammalian homologue of the Drosophila gene Diaphanous 1 (mDia1).

These ECM fibrous proteins are particularly long-lived, and they are potential targets of glycation. The impact of glycation on ECM functionality is mainly focused on two main mechanisms, by modifying molecular recognition at specific protein binding sites (24), or by altering the mechanical properties due to AGE crosslinks of load-bearing protein such as collagens, leading to stiffening of tissues (25).

A growing body of both clinical and experimental evidences suggests that tissue mechanics is a key modulator of tumor progression and clinical outcome, and a tight relationship has been reported between ECM remodelling and stiffening, cellular mechanosignaling, tissue inflammation and tumor aggression (26).

Of note, tumor-associated ECM remodeling leading to the stiffening of tumor microenvironment is mainly mediated by ECM deposition, fiber alignment and crosslinking, which, in turn, is able to promote tumor progression and malignancy through increased integrin signaling (27). Stiffened ECM also enables key tumor-suppressing mechanisms to be bypassed (28). Furthermore, the stiffened tumor ECM permits tumor cells to not only overcome contact inhibition and survive but also to sustain high rates of proliferation (29).

Stiffening, can also induce highly invasive cell phenotypes, and to promote transforming growth factor (TGF)-β-induced epithelial–mesenchymal transition (EMT) (30,31). In this context,

the invadopodia formation, which is a key process for guiding cell migration is also sensitive to ECM rigidity (32).

Of note, matrix crosslinking is one of the main mechanisms by which the tumor stroma stiffens during solid tumor progression (33,34).

Additionally, increasing collagen matrix stiffness via non-enzymatic glycation can also alter vascular growth and integrity, mimicking the changes that exist in the tumor vasculature structure (35). Furthermore, increased ECM stiffness also promotes metastatic cancer cell interaction with the endothelium and thus favoring cancer metastasis (36).

AGE-induced crosslinking of fibronectin is another mechanism to promote matrix accumulation by increasing the stiffness of collagen and reducing fibril breakage by shear forces (37).

AGE-mediated crosslinking of the collagen IV and laminin promotes the stiffening of basal lamina matrix, thus favoring the invasiveness of tumor cells and cancer progression (38).

Additionally, tumors rely primarily anaerobic metabolism and show a higher rate of glucose uptake and glycolysis. This metabolic reprogramming unavoidably favors AGEs formation in cancer cells (39–41), thus leading to a higher local formation of AGEs, which is turn may favor the *in situ* formation of tumor ECM crosslinking.

## Glycated ECM and RAGE activation: a missing piece in the puzzle

The cancer-associated ECM is not only an essential and integral component of tumors, but also an active contributor to their histopathology and behavior. Abnormal ECM affects cancer progression by directly promoting cellular transformation and metastasis (23,42). At present, the modification of ECM components by AGEs has been suggested to be a relevant factor promoting matrix remodeling and/or dysfunction. However, these modifications have been mostly associated to mechanical changes, such as crosslinks which may then render a stiffened matrix. As tumors develop stiffness increases over time, due largely to ECM remodeling, and this stiffness even correlates well with disease progression (43). Noteworthy, it has become increasingly clear that the stiffened ECM is not a merely passive by-product of malignancy, but rather these physical changes actively participate not only in tumor progression but also in how tumors respond to therapy (44).

At present, the molecular mechanisms described to explain how matrix stiffening may promote tumor growth and invasiveness have been mainly ascribed to mechanotransduction mechanisms where cells sense and convert exogenous forces into signaling pathways. However, the contribution to tumor progression of RAGE-dependent mechanisms triggered by a highly glycated and stiffned ECM are missing.

The major constituents of ECM are fibrous-forming proteins such as collagens, elastins, laminins and fibronectin (23). Noteworthy, all these proteins are targets of the Maillard reaction and thus become highly glycated in diabetes/hyperglycemia, which may then become as a potential source of AGEs-modified proteins, and the subsequent activation of RAGE-dependent mechanisms (See Figure 2).

The biological consequence of RAGE activation mechanisms seems to be connected in different ways to drive some hallmarks of cancer onset and tumor growth (Figure 2B). Next, we summarize the topics we intend to deal with this connection and where a mechanistic approach reporting the existence of RAGE-dependent mechanisms induced by glycated ECM is missing.

### Sustained growth

A common feature of both cellular transformation and tumor progression is to escape from proliferative suppression, resulting in sustained cell proliferation and cell signaling (33). It is known that cell cycle transition from G1 to S phase requires cellular adhesion to the ECM through Erk signaling and cyclin D1 induction (45). Of note, the RAGE signaling network triggered by engagement by glycated proteins includes the recruitment of signaling mediators such as Erk, PI3K, Rac and cyclin D1 (16,46). Additionally, malignant tissue is typically stiffer than its normal counterpart and this altered biochemical property is largely mediated by a cross-linked collagenous ECM. In response to a stiffened matrix cells are able to activate Erk, PI3K and Rac signaling, in order to accelerate cell cycle progression through increased expression of cyclin D1 (47,48).

Importantly, advanced glycation-mediated collagen crosslinking has been observed to stiffen tissues in different diseases (49,50). Furthermore, matrix stiffness has been reported to induce the expression of miRNAs that lower expression of the tumor suppressor PTEN, thereby enhancing the PI3K/Akt activity to promote cell growth and survival (28).

Any neoplastic lesion must overcome the limitations imposed by tumor suppressors. For instance, Smad phosphorylation by TGF-β induces p21 and p27, which, in turn, inhibit the activity of critical cyclin-dependent kinases needed for cell cycle progression (51).

In many tumors, the cell–ECM interactions can regulate TGF-β signaling by inducing p130Cas, which in turn prevents Smad3 phosphorylation and thus reducing p15 and p21 expression (52). This finding may explain the mechanisms underlying the resistance to TGF-β-induced growth suppression seen in many cancers (53,54).

Collagen type I is a major component of interstitial connective tissues and constitutes up to 90% protein content (55). Very recently, it was shown that aged collagen, which is highly rich in AGEs content, promotes the proliferation of human fibrosarcoma HT-1080 cells by decreasing p21 expression and impairing the discoidin domain receptor-2-mediated tumor cell growth suppression (56). Noteworthy, collagen aging has been ascribed to the accumulation of structural changes associated with the extent of advanced glycation-modified motifs (57).

All these data have been only ascribed to changes in mechanical features of ECM, but there are no reports denoting the activation of RAGE-dependent mechanisms.

### Promoting autophagy

In the rapidly growing stage of tumor development, angiogenesis by itself is not able to satisfy the great demand of amino acids, oxygen and growth factors for fast-proliferating tumor cells. Autophagy can digest damaged proteins, organelles and other macromolecules and recycle cytoplasm materials and thus adding a fresh input to balance the demand of nutrients and energy (58).

Tumor cells activate autophagy in response to cellular stress and/or increased metabolic demands related to rapid cell proliferation. Autophagy-related stress tolerance can enable cell survival by maintaining energy production that can lead to tumor growth and, more interestingly, to therapeutic resistance (59). Furthermore, evidence indicates that the predominant role of autophagy in cancer cells is to confer stress tolerance, which serves to maintain tumor cell survival (60). Knockdown of essential autophagy genes in tumor cells has been shown to confer or potentiate the induction of cell death (61). This is particularly interesting, considering that diabetics who develop cancer

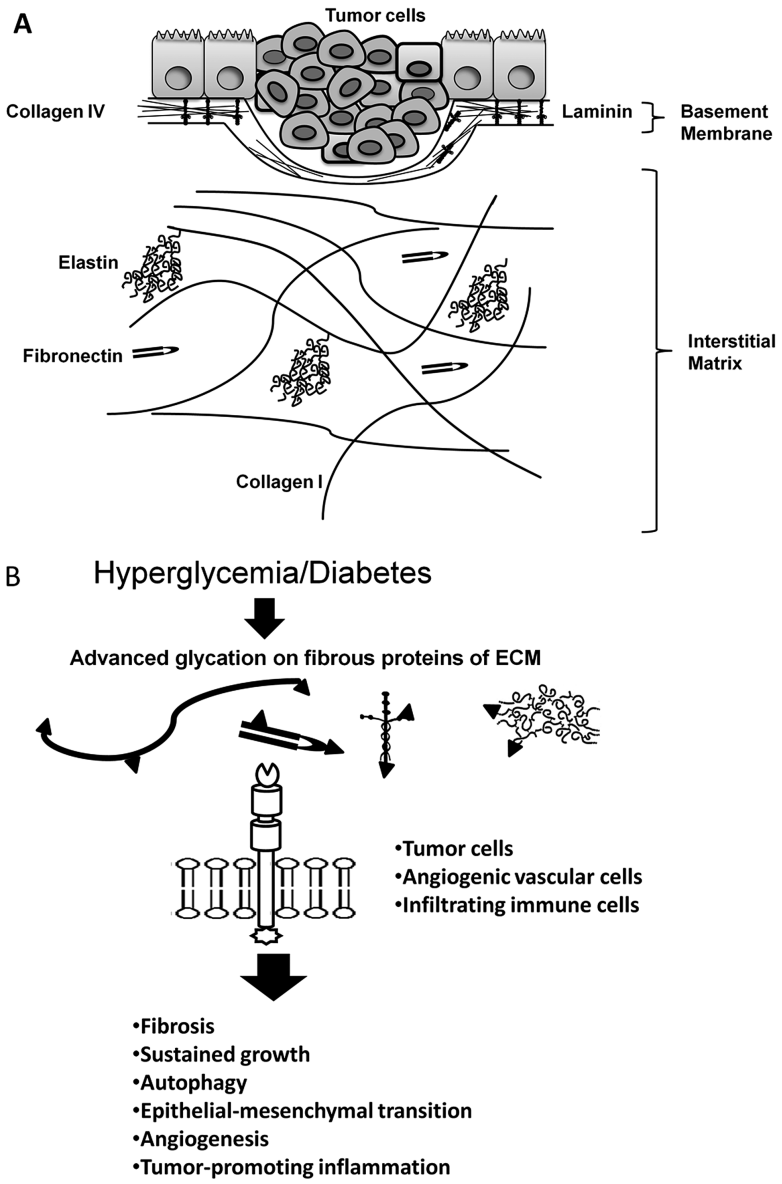


**Figure 2.** The major constituents of ECM are long-live and fibrous-forming proteins such as collagens, elastins, laminins and fibronectin (**A**). Under conditions such as sustained hyperglycemia/diabetes (**B**) all these proteins become highly glycated, which may then become as a potential source of AGEs-modified proteins, and the subsequent activation of RAGE-dependent mechanisms, not only on tumor cells but also on other RAGE-bearing cell types within the tumor microenvironment leading to increased fibrosis, inflammation and angiogenesis The biological consequence of RAGE activation mechanisms seems to be connected in different ways to drives some hallmarks of cancer onset.

have a worse prognosis after chemotherapy or surgery (5–7). Recently, it was demonstrated that RAGE-mediated tumor cell survival to some chemotherapeutic agents is associated with increased autophagy, resulting in a decreased phosphorylation of mammalian target of rapamycin and increased Beclin-1/VPS34 autophagosome formation. Although these initial reports were raised by the activation of RAGE-dependent mechanisms induced by the alarmin HMGB1, very recently published data indicate that activation of RAGE by soluble AGEs is also able to promote autophagy in different cell types (62–64).

Different fibrous matrix proteins are rapidly emerging as regulators of autophagy (65). Of particular importance, all these proteins become highly glycated in diabetes and no data are available linking the promotion of autophagy with the activation of RAGE by ECM glycation.

## Epithelial–mesenchymal transition

Tumors often display desmoplasia and this fibrotic state is characterized by increased deposition and altered organization and enhanced post-translational modification of ECM proteins. Furthermore, chronic fibrosis predisposes the affected tissues to develop cancer, but also correlates with poor prognosis, and it is also believed to enhance tumor progression (31,66).

Interestingly, the contribution of AGEs to the modification of matrix proteins, its consequences in the disruption of ECM dynamics, and the generation of a profibrotic profile, has been extensively studied in the context of many complications of diabetes (67,68). Of note, in the heart glycated collagen has been shown to stimulate alpha11 integrin expression, the major fibrillar collagen receptor, through a Smad3-dependent

and TGF-β2-regulated signaling pathway, and thus favoring the fibrotic response observed in diabetic cardiomyopathy (69).

EMT is a form of cell plasticity in which epithelia acquires mesenchymal phenotypes and is increasingly recognized as an integral aspect of tissue fibrogenesis. Noteworthy, glycated ECM has been shown to promote EMT in kidney and lung epithelial cells (70,71). Additionally, AGEs in the lens capsule promote the TGF-β2-mediated EMT of lens epithelial cells, thereby contributing to cataract formation by a RAGE-dependent mechanism (72).

EMT has also emerged as a critical process for the acquisition of migration and invasiveness and a pluripotent stem-cell-like phenotype and thus playing a pivotal role in the metastatic process (73). It is well-known that metastasis is the main cause of death in 90% of patients carrying solid tumors.

ECM stiffness promotes TGF-β-induced EMT and induces a basal-like tumor cell phenotype to stimulate cancer metastasis (74). Noteworthy, advanced glycation-mediated collagen crosslinking is known to produce stiffened tissues in different diabetes-related diseases. Once more, biological activity has been mainly ascribed to changes of mechanical nature and the role of RAGE activation by glycated ECM to promote EMT remains to be elucidated.

## Angiogenesis

Tumor cells and tumor-associated stroma are sources of vascular endothelial growth factor, which is responsible for vascular proliferation and altered permeability of newly formed vessels (75). On note, glycated albumin has been reported to markedly increase vascular endothelial growth factor protein expression levels in different cancer cell types (76).

We and others have reported that RAGE engagement by soluble ligands, mainly glycated soluble proteins, induces profound effects on endothelial cells, including up-regulation of vascular endothelial growth factor and metalloproteinase-2, as well as the disruption of VE-cadherin–catenin complex, thus favoring capillary tube formation (77,78). Additionally, AGE–RAGE interaction also reduces the pericytes number which in turn relieves the restriction on endothelial cell replication and facilitates angiogenesis (14).

## Tumor-promoting inflammation

In the nineteenth century, Rudolph Virchow first launched the idea about a putative connection between inflammation and cancer. At present, resurgent research interests on this topic have raised a growing body of evidence supporting the contribution of chronic inflammation to the development of malignancies, as well as the association between the usage of non-steroidal anti-inflammatory agents and protection against various tumor types (79,80).

AGE-mediated activation of RAGE results in the increased activation of pro-inflammatory transcriptional regulators, including nuclear factor-kappa B (NF-kB), signal transducer activator of transcription 3 (STAT3) and hypoxia inducible factor 1 (HIF-1). Increased activation of these critical transcription factors increases the secretion of cytokines/chemokines by stromal cells and thus leading to the recruitment and activation of inflammatory cells into the tumor microenvironment (20,81). Interestingly, a chronically inflamed tissue is often fibrotic and shows increased collagen and fibronectin deposition. The tumor microenvironment thus becomes both a fibrotic and inflammatory niche (82–84).

Situations of chronic inflammation can promote genomic instability leading to DNA damage, oncogene activation or impaired function of tumor suppressors. In this sense, nucleotide sequence modification through single base editing is emerging as an important player in tumorigenesis (85). Activation-induced cytidine deaminase is a member of the cytidine deaminase family (86). Activation-induced cytidine deaminase expression is induced by stimulation of proinflammatory cytokines such as TNF-alpha in several cell types, through the activation of NF-kB, thereby it is now considered as a DNA mutator that contributes to inflammation-related tumorigenesis (87). As already mentioned, RAGE activation can evoke the production of different pro-inflammatory cytokines, including TNF-alpha through activating NF-kB pathway.

MicroRNAs (miRNAs) are small non-coding single-stranded RNAs, which are highly conserved during evolution, and controls the gene expression by degrading the corresponding mRNA, destabilizing and/or inhibition their translation. Of note, miRNAs can act as onco-miRNAs or anti-onco-miRNAs depending on their potential target genes (88). Furthermore, some miRNAs have been reported to be involved in different cancer hallmarks, including cancer-related inflammation (89).

Due to the proinflammatory nature of RAGE activation, and previous reports showing how some miRNAs markedly changed their expression profiles after RAGE activation, it is tempting to speculate about the possibility of either the repression of tumor suppressor miRNAs or the activation of onco miRNAs in a RAGE-mediated inflammation-dependent manner.

## Concluding remarks

At present, an extensive body of epidemiological studies suggests that people with diabetes/hyperglycemia have an increased risk of developing certain cancer types. Furthermore, patients with diabetes who develop cancer have even a worse prognosis after treatment with chemotherapy or surgery. Although hyperglycemia is one of the most widely studied metabolic changes in diabetes mellitus, the effects of hyperglycemia on cancer have received much less attention. One of the chronic complications of high levels of blood glucose is the irreversible glycation of proteins and lipids leading to the formation of AGEs.

The modification of ECM components by AGEs has been denoted to be a relevant factor in promoting matrix remodeling and/or dysfunction. This appraisal has been mainly focused on mechanical changes induced by AGE-mediated crosslinking, which in turn promote the stiffening of the ECM, and thus inducing mechanoreceptors-based mechanisms, which favor tumor growth and invasiveness. A major group of receptors to mediate these effects are member of the integrin family, present both on tumor cells and the different cell types in the microenvironment including cancer-associated fibroblasts (90).

However, the potential role of RAGE-mediated mechanisms triggered by glycated ECM components remains to be elucidated. Finally, potential therapeutic approaches have emerged during the last decade by using either pharmacological inhibitors of AGE formation and/or agents that break established AGE crosslinks between proteins of ECM. All these agents can be used as relevant tools on both preclinical and clinical studies for unraveling the potential contribution ECM glycation by triggering RAGE-depended mechanisms on cancer onset.

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